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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,597	09/25/2003	Alexa L. Martinez	2057.0040002	1312

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
10/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,597	MARTINEZ ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-26,35-38,59-77,79-81,90-96 and 109-139* is/are pending in the application.

4a) Of the above claim(s) *36,37,91,92,112,115-117,120,123-125 and 134-139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/09; 4/15/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1-21,23-26,35,38,59-77,79-81,90,93-96,109-111,113,114,118,119,121,122 and 126-133.

DETAILED ACTION

1. The indicated allowability of claims 1-26, 35-38, 59-77, 79-81, 90-96, 109-139 is withdrawn in view of the newly discovered reference(s) to Lee et al. (US4261973). Rejections based on the newly cited reference(s) follow.

Information Disclosure Statement

2. The information disclosure statement filed 10/1/09 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Note that an explanation was not provided for JP 2002-527491, JP 50-42087, JP 53-24033. These references have been placed in the file but have not been considered.

Election/Restrictions

3. An election was conducted in this Application on 10/10/2005 with an election of species. Applicants properly responded to the election of species and elected the species GM-CSF, dihydroxy polyethylene glycol. Since this case has been withdrawn form issue, the restriction is again reinstated. Based on the election, claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-110, 113, 118, 121, and 126-133 read on the elected species and have been examined. Note that other prior art has been applied that anticipate claims. Based on the application of these art, the claims examined include 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-111, 113-114, 118-119, 121-122, and 126-133. Claims 36-37, 91-92, 112, 115-117, 120, 123-125, 134-139.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-111, 118-119 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (US4261973).

The claims are drawn to a conjugate comprising bioactive component covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end.

Lee et al. teaches a two batches of polyethylene glycol (PEG, from Baker Chemical Co., Phillipsburg, N.J.), with average molecular weights of 6,000 and 20,000, referred to hereafter as PEG.sub.6 and PEG.sub.20, respectively, were coupled to ovalbumin or and ragweed pollen allergens using cyanuric chloride as the coupling agent (see example 1-2). Note that the reference does not teach that the peg group is methoxylated and thus it would have a distal hydroxyl group at the distal end. Note that the ovalbumin meets the limitation of claim 26 and 35. The reference also teaches that the poly ethylene glycol has a molecular weight between 2000-35000 daltons (see claim 2). The disclosure of the example of 6000 and 20000 and the fact that the glycol can have a molecular weight between 2000-35000 daltons meets the limitation of the molecular weight range. It is noted that the prior art does not teach the specific reactants of PEG or the method of making as claimed in claim 59. However, the reference still anticipates the claimed invention because the prior art teaches the claimed final product, i.e. to a conjugate comprising bioactive component

covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end. The MPEP states "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP 2113.

The reference anticipates the claimed invention.

5. Claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-110, 114, 118, 122 are rejected under 35 U.S.C. 102(b) as being anticipated by Pepinsky et al. . (WO00/23114).

The claims are drawn to a conjugate comprising bioactive component covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end.

Pepinsky et al. teaches modification of interferon with a polymer (see page 17). The reference states that the polymer utilized contains at least one terminal hydroxyl group (see page 19). The reference specifically teaches the reaction of PEG-aldehyde with interferon (see page 19-20). The reference teaches numerous polymers can be used such as PEG and their molecular weight is between 300-100000 or between 10000-40000 (See page 21-22). The reference exemplifies a specific reaction where to a 1 mg/ml solution of the interferon-beta-1a from the SP eluate, 0.5 M sodium phosphate pH 6.0 was added to 50 mM, sodium cyanoborohydride (Aldrich, Milwaukee, Wis.) was added to 5 mM, and 20K PEG aldehyde (Shearwater Polymers, Huntsville, Ala.) was added to 5 mg/ml. The sample was incubated at room temperature for 20 hours. The pegylated

interferon was purified from reaction products by sequential chromatography steps on a Superose.RTM. 6 FPLC sizing column (Pharmacia) with 5 mM sodium phosphate pH 5.5, 150 mM NaCl as the mobile phase and SP-Sepharose.RTM. FF. The sizing column resulted in base line separation of modified and unmodified interferon beta (chromatograph not presented here). The PEG-interferon beta-containing elution pool from gel filtration was diluted 1:1 with water and loaded at 2 mg interferon beta/ml resin onto an SP-Sepharose.RTM. column. The column was washed with 5 mM sodium phosphate pH 5.5, 75 mM NaCl and then the pegylated interferon beta was eluted from the column with 5 mM sodium phosphate pH 5.5, 800 mM NaCl. Elution fractions were analyzed for protein content by absorbance at 280 nm. The pegylated interferon concentration is reported in interferon equivalents as the PEG moiety did not contribute to absorbance at 280 nm (see example 2). Note that the reference teaches the use PEG aldhyde, which meets the limitation of monoaldehyde of claim 6. Thus, the conjugate produced would have a distal hydroxyl group. Note that the reference polymer utilized contains at least one terminal hydroxyl group. It is noted that the prior art does not teach the specific reactants of PEG or the method of making as claimed in claim 59. However, the reference still anticipates the claimed invention because the prior art teaches the claimed final product, i.e. to a conjugate comprising bioactive component covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end. The MPEP states "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP 2113.

Since the reference teaches a pegylated interferon where the peg group contains a distal hydroxy group, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-21, 23-26, 35, 38, 59-77, 79-81, 90, 93-96, 109-110, 113, 118, 121, and 126-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado (US5349052) in view of Zalipsky et al. and Pepinsky et al. . (WO00/23114).

The claims are drawn to a conjugate comprising bioactive component covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end.

Delgado et al. teaches pegylated GM-CSF (see abstract). The reference discloses pegylation of GM-CSF increases plasma half life (see col. 1). The reference states that coupling of PEG to

proteins oupling of PEG to proteins is usually achieved by activation of the hydroxyl groups of PEG w

th a suitable reagent that can be fully substituted by nucleophilic groups in the protein (mainly lysine E-amino groups) (See col. 2, lines 40-44). The PEG utilized in the reference is mPEG which results in the presence of a methoxy in the distal end of the PEG group. The difference between the prior art and the instant application is that the reference utilizes mPEG rather than a PEG with a distal hydroxyl group.

However, Zalipsky et al. teaches that PEG groups can be attached to increase half life (see page 1177). The reference states in order to make possible the attachment of drugs having other functional groups such as amino or hydroxyl, there was a need to preparing PEG having other functional end groups. The reference specifically teaches pegylation using PEG-COOH which conjugated to the active agent through amide bonds (see page 1181).. Note that the use of such a PEG would contain a distal OH on the PEG.

Pepinsky et al. teaches modification of interferon with a polymer (see page 17). The reference states that the polymer utilized contains at least one terminal hydroxyl group (see page 19). The reference specifically teaches the reaction of PEG-aldehyde with interferon (see page 19-20). The reference teaches numerous polymers can be used such as PEG and their molecular weight is between 300-100000 or between 10000-40000 (See page 21-22). The reference exemplifies a specific reaction where to a 1 mg/ml solution of the interferon-beta-1a from the SP eluate, 0.5 M sodium phosphate pH 6.0 was added to 50 mM, sodium cyanoborohydride (Aldrich, Milwaukee, Wis.) was added to 5 mM, and 20K PEG aldehyde (Shearwater Polymers, Huntsville, Ala.) was added to 5 mg/ml. The sample was incubated at room temperature for 20 hours.

It would have been obvious to pegylated the GM-CSF using either PEG-COOH or PEG-aldheyde because such PEG groups have been utilized in the art to pegylate therapeutic molecules. There would have been a reasonable expectation of success because such both PEG-COOH or PEG-aldehyde would allow for conjugation of PEG to a amine for the formation of an amide bond.

Note that the reference polymer utilized contains at least one terminal hydroxyl group. It is noted that the prior art does not teach the specific reactants of PEG or the method of making as claimed in claim 59. However, the reference still anticipates the claimed invention because the prior art teaches the claimed final product, i.e. to a conjugate comprising bioactive component covalently attached to one linear or branched polyalkylene glycol, where the polyalkylene glycol contain a hydroxyl group at the distal end. The MPEP states "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP 2113.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANISH GUPTA whose telephone number is (571)272-0965. The examiner can normally be reached on 5/4/9.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654